ADDRESSING THE GLOBAL BURDEN OF CHRONIC KIDNEY DISEASE THROUGH CLINICAL AND TRANSLATIONAL RESEARCH

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ABSTRACT

Worldwide, an estimated 200 million people have chronic kidney disease (CKD). In the United States, African Americans (AAs) have a four-fold excess risk of CKD compared to non-Hispanic white people and globally, people in the low-to-middle income countries of Asia and Sub-Saharan Africa have the highest rates of CKD. Annually, more than 500,000 individuals develop end-stage renal disease (or CKD stage 5) in Sub-Saharan Africa alone and the vast majority of these patients suffer premature mortality. The health care costs and economic burden of CKD are huge and not sustainable even in advanced Western countries. A recent discovery on the role of Apolipoprotein 1 (*APOL1*) G1 and G2 renal risk variants in AAs has a huge potential to unravel the etiology of CKD in both AA and other black populations. Under the National Institutes of Health (NIH)−sponsored Human Heredity and Health in Africa (H3Africa) initiative, a large prospective genetic study of CKD is being conducted in 8000 participants in four African countries (Ethiopia, Ghana, Kenya, and Nigeria; for a total population of 320 million). This and other basic research studies in the United States could potentially shed great insight into the genetics and biologic mechanisms involved in the excess predilection of Africans and AAs to CKD.

INTRODUCTION

Chronic kidney disease (CKD) is classified into five stages (stages 1–5) according to the level of urinary protein excretion and renal function as measured by the estimated glomerular filtration rate (eGFR) which is derived from age, race, sex, and serum creatinine concentration (1). End-stage renal disease (ESRD) which corresponds to an eGFR of <15 mL/min/1.73m (2), initiation of maintenance dial-

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ysis or receipt of preemptive renal transplantation is classified as CKD stage 5. In the United States, African Americans are at increased risk for all stages of CKD with the gap in cumulative risk between African Americans and Caucasians increasing in parallel with the severity of CKD (2–4). The incidence of ESRD (CKD stage 5) is 783 per million population in African Americans compared to 295 per million population in non-Hispanic Whites (5). The cumulative lifetime risk of ESRD is 7.5% in African Americans and 2.1% in Caucasians (6). All stages of CKD are associated with increased health care use and ESRD treatment alone costs the Medicare program $35 billion per year or approximately 6.3% of the annual Medicare expenditure even though ESRD patients account for only 1% of the total population of Medicare beneficiaries (7). Beginning from CKD stage 3, overall mortality and cardiovascular-specific mortality increases to three to 13 times higher than that of the general population and, by the onset of ESRD, the annual death rate is 17% to 20% (5,8).

On a global level, the burden of CKD continues to increase (9,10). Low- to middle-income countries are undergoing epidemiologic transition typified by a relative increase in the burden of noncommunicable chronic diseases (such as diabetes mellitus, obesity, hypertension, cardiovascular disease and CKD) as the prevalence of infectious diseases diminishes with improved sanitation and immunization programs (10–11). Globally, more than 100 countries (with combined population >1 billion) have no provisions for chronic maintenance dialysis or kidney transplantation and thus, more than 1 million people die annually from ESRD (11–13). Kidney disease imposes disproportionate, incalculable human suffering and a catastrophic economic burden on the African continent in several respects: less than 2% of the patients with ESRD have access to renal replacement therapy (ie, dialysis or kidney transplantation), making ESRD a death sentence for most patients; the age of onset of ESRD is ~20 years earlier in African populations compared to developed Western countries (45 years vs 63 years); the ESRD rate is increasing at 6% to 8% per year on the African continent; Africa is experiencing an accelerated incidence of hypertension (60 million people) and type 2 diabetes mellitus (>12 million people), which are the underlying causes in >15% of CKD cases; and finally, at current projections, none of the 54 countries in Sub-Saharan Africa (SSA) will be able to afford the cost of medical care associated with predialysis CKD for their populations (estimated to be $2500 to $20,000 per patient annually) (9,14–18). Even more out of reach is the annual cost of dialysis treatment which amounts to $20,000 to $30,000 per person per year in SSA — Medicare covers this cost expenditure for

the 500,000 US citizens with ESRD. In contrast, fewer than 5% of the 500,000 new cases of ESRD in SSA gain access to even a limited period of dialysis (15). These distressing facts elevate the urgent need for research to mitigate the incidence and severity of kidney disease globally and particularly in SSA.

Beginning with the establishment of the US Renal Data System (USRDS) by the National Institute of Diabetes, Digestive and Kidney Disease (NIDDK) under the leadership of Dr Larry Agodoa in the mid-1980s, the United States has made concerted and intensive efforts to address the extraordinarily high burden of kidney disease in African Americans (AAs). One major undertaking was the NIDDK-funded African American Study of Kidney Disease and Hypertension (AASK, 1994 to 2009) (19–21). In this multicenter clinical trial and cohort study, 1094 AAs with kidney disease due to hypertension were treated with different classes of antihypertensive regimen with aims towards two blood pressure goals. The AASK 10-year follow-up showed that even with optimal blood pressure control and the use of ramipril, an angiotensin converting enzyme inhibitor which acts by blocking the renin angiotensin aldosterone system, 53.9% of AASK participants ultimately developed kidney failure, cardiovascular events, or died (20). This finding is alarming because the AASK participants were not spared from relentless progression of CKD despite using state-of-the-art drug therapy and achievement of the best blood pressure levels of any antihypertensive clinical trial ever performed (20).

In 2008, investigators used techniques that examined ancestry informative markers to localize risk for nondiabetic nephropathy to a region on chromosome 22q12 spanning the *MYH9* gene region (22). Out of 10 markers, the MYH9 as well as several haplotypes (E, S, and F) showed strong association signals in AAs. These risk haplotypes are present at high frequencies in populations of West African descent, but have low frequencies in other populations. Subsequent fine mapping by other groups pointed to G1 (Ser342Gly or rs73885319) and G2 (rs71785313) variants in the nearest neighboring gene *APOL1* as the candidate causal variants for the chromosome 22 signal (23). This region on chromosome 22q12 shows evidence of recent (10,000 years) positive selection associated with trypanosomiasis in individuals of West African descent, including AAs. In 2010, it was reported that AAs who have ESRD of nondiabetic etiology (hypertension and focal segmental glomerulosclerosis [FSGS]) were seven to10 times more likely to have one of two independent sequence variants in the *APOL1* gene on chromosome 22 (24–27). A growing body of evidence suggest that genetic susceptibility also plays a key role in the etiology of nephrop-

athy due to type 2 diabetes mellitus (T2DM) (28–31). For example, Schelling et al found strong evidence of linkage between the intermediate quantitative trait of T2DM (renal function) and chromosomes 11p15.1 (31). A genome-wide scan in 206 AA sibling pairs with T2DM also identified susceptibility loci on chromosomes 3q, 7p, and 18q (31, 32). Collectively, these studies indicate a critical genetic component in the etiology of ESRD which may explain up to 80% of the excess cases of CKD in all African American populations studied, although these studies included a small numbers of black patients from in SSA (16, 33, 34).

GLOBAL EPIDEMIOLOGY OF CKD

In the United States, treated ESRD has increased steadily over the past 2 decades. In 2005, 485,000 individuals in the United States underwent treatment for ESRD with a mortality rate of 167/1000 patient-years and costs exceeding 20 billion dollars (35). Current estimates suggest that approximately 26 million Americans have CKD (36). Data extrapolation based on the National Health and Nutrition Examination Surveys (NHANES), shown in Table 1, indicate that the prevalence of CKD stages 1 to 4 increased from 10.0% in 1988–1994 to 13.1% in 1999–2004 with a prevalence ratio of 1.3 (95% confidence interval [CI], 1.2–1.4). The prevalence estimates of CKD stages during 1988–1994 and 1999–2004, respectively, were 1.7% and 1.8% for stage 1; 2.7% and 3.2% for stage 2; 5.4% and 7.7% for stage 3, and 0.21% and

TABLE 1
Prevalence of CKD Stages 1–4 in US Adults Aged 20 Years or Older Based on NHANES 1988–1994 and NHANES 1999–2004[a]

CKD Stage[b]	Prevalence (95% CI)		Prevalence Ratio for NHANES 1994–2004 to 1988–1994 (95% CI)	Estimated No of US Adults in 2000, No in Millions (95% CI)
	NHANES 1988–1994	NHANES 1999–2004		
1	1.71 (1.28–2.18)	1.78 (1.35–2.25)	1.05 (0.85–1.30)	3.6 (2.7–4.5)
2	2.70 (2.17–3.24)	3.24 (2.61–3.88)	1.21 (1.03–1.41)	6.5 (5.2–7.8)
3	5.42 (4.89–5.95)	7.69 (7.02–8.36)	1.42 (1.25–1.62)	15.5 (14.1–16.8)
4	0.21 (0.15–0.27)	0.35 (0.25–0.45)	1.70 (1.11–2.51)	0.7 (0.5–0.9)
Total	10.03 (9.16–10.91)	13.07 (12.04–14.10)	1.30 (1.19–1.43)	26.3 (24.2–28.3)

Abbreviations: CKD, chronic kidney disease; CI, confidence interval; NHANES, National Health and Nutrition Examination Surveys.

[a]Adapted from Coresh et al.[36]

[b]Definition based on standard criteria[1]: stage 1, persistent albuminuria with glomerular filtration rate (GFR) higher than 90 mL/min/1.73m^2; stage 2, persistent albuminuria with GFR of 60–89 mL/min/1.73m^2; stage 3. GFR of 30 to 59 mL/min/1.73m^2; stage 4, GFR of 15 to 29 mL/min/1.73m^2. The age-adjusted prevalence rates for CKD stages 1, 2, 3, and 4 in 1998–1994 adjusted to the 1999–2004 age distribution are 1.7%, 2.8%, 5.6% and 0.2%, respectively, for a total of 10.3%.

0.35% for stage 4. The Center for Disease Control (CDC) analysis of NHANES data also indicates that the prevalence estimates for CKD are strongly related to age, gender, race, and several other clinical and demographic factors (37). Strikingly, non-Hispanic black and Mexican-American people have a higher prevalence of CKD than other racial/ethnic groups and the elderly also have a substantial reservoir of CKD compared to other age groups in the United States (37).

There are nearly 700,000 people with ESRD in the United States corresponding to an annual incidence rate of 355 per million population (pmp) (7). In the United Kingdom (UK) and in Europe, the average annual incidence of ESRD is 120,000 and 135,000, respectively (38). The age-adjusted incidence rate of ESRD in India is estimated to 229 pmp (39). Saudi Arabia reports a prevalence rate of 5.7% (40). Data from Australia showed that 6% of the population have some form of CKD, and across SSA, prevalence estimates range from 3% to 19% depending on CKD stages have been estimated (16,40). The increasing burden of CKD parallels the phenomenal increases in the prevalence of T2DM and hypertension across the globe (16,41). People with ESRD represent only a small fraction of the overall CKD population. For example, in the United States, the overall prevalence of CKD (26 million) is 50-fold higher than the number of individuals who are receiving chronic maintenance dialysis therapy or who have received a kidney transplant (7). CKD at all stages is associated with increased cardiovascular event rates, health care use, and overall premature mortality (8,42). Life expectancy is reduced by as much as 10- to15-fold in patients who have ESRD (43,45). The cost of dialysis therapy or kidney transplantation is prohibitive ranging from USD $15,000 in SSA to more than $80,000 in the United States (7,16,46). The immense morbidity, lost life years, and economic burden of CKD have galvanized CKD prevention programs globally (41,47). The United States and many western countries have instituted large-scale research programs aimed at understanding etiologic risk factors and the mechanisms of CKD progression and identifying new therapeutic targets (48–51).

APOLIPOPROTEIN L1 GENE NEPHROPATHY

Traditional risk factors alone do not adequately explain the disparity in CKD burden between AAs and other ethnic groups in the United States (52). Recently, Kopp et al reported techniques that examined ancestry informative markers to localize risk for nondiabetic nephropathy to a region on chromosome 22q12 spanning the *MYH9* gene region

(22,53,54). Out of 10 *MYH9* markers, several haplotypes (E, S, F) showed strong association signals in AAs. The risk haplotype is present at high frequencies in populations of West African descent, but has low frequencies in other populations. Subsequent fine mapping by other groups indicated G1 (Ser342Gly or rs73885319) and G2 (rs71785313) variants in the nearest neighboring gene apolipoprotein L1 (*APOL1)* as the candidate causal variants for the chromosome 22 signal. This region on chromosome 22q12 shows evidence of positive selection in individuals of West African descent, including AAs. *APOL1* is one of six closely related apolipoprotein L family member genes clustered on chromosome 22 and is restricted to the genomes of humans and some nonhuman primates. Circulating *APOL1* associates with high density lipoprotein 3 (HDL_3) particles and functions as a trypanolytic factor in human serum. The parasite endocytoses *APOL1*-containing HDL particles, and once internalized, *APOL1* is targeted to the lysosome, where its colicin-like pore forming activity causes osmotic swelling of the lysosome and trypanosome death. Trypanosome species that infect humans and cause disease have adapted to inhibit *APOL1*-mediated trypanolysis. Variant *APOL1*, which encodes the kidney disease risk variants, can kill disease-causing trypanosomes by circumventing the parasite's mechanism to evade lysis. The parasite killing effect is dominant, requiring a single copy of the risk variant *APOL1* gene, whereas association with kidney disease is best fit by a recessive model. Because resistance to trypanosomal infection is a selective advantage in endemic regions, the kidney disease risk-variants of *APOL1* have been maintained in African populations. Consistent with this premise, the region of chromosome 22 that contains *APOL1* shows evidence for positive selection. Similar to sickle cell disease, the heterozygous state for *APOL1* kidney disease-associated variants is advantageous, but the homozygous state can result in disease progression. Variants near UMOD, MTHFR, and PKARG2 show highly significant association in Caucasian populations with CKD (55). These variants have not been assessed in people living in SSA.

Since the association between *APOL1* and kidney disease in AAs was first described in 2010 (23), several studies have confirmed that *APOL1* increases the risk of development of ESRD in nondiabetic CKD among AAs (Table 2) (26,54,56,57). AAs with two GI or G2 *APOL1* risk alleles have 12- to 18-fold higher risk of nondiabetic ESRD as compared to non-Hispanic white people (58–60). The greatest impact of *APOL1* risk variants is on HIV-associated nephropathy (HIVAN) for which AAs with two alleles of the *APOL1* renal risk variants have a

TABLE 2
APOL1 Genetic Variants and the Risk of Kidney Disease in African Americans

Population and Etiology	Variant	Odds ratio	*P* Value	Sample Size Cases/controls	Reference
Nondiabetic ESRD	G1	4.9	3.50×10^{-04}	346/140	Tzur et al[23]
Biopsy-proven FSGS	G1 or G2	10.5	4.38×10^{-07}	192/176	Genovese et al[24]
Hypertensive ESRD	G1 or G2	7.3	1.0×10^{-63}	1,002/923	Genovese et al[24]
ARIC*	G1 or G2	2.43	.05	2663/404	Foster et al[57]
CRIC/AASK	G1 or G2	1.88	<.001	AASK, n = 693 CRIC, n = 2955	Parsa et al[62]

*Incidence rate ratio of CKD among 3067 ARIC participants with no CKD at inception with up to 25 years of follow-up.

Abbreviations: ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; ARIC, atherosclerosis risk in communities; CRIC, Chronic Renal Insufficiency Cohort study; AASK, African American Study of Kidney Disease and Hypertension; CKD, chronic kidney disease.

29-fold higher risk of HIVAN compared to HIV-infected AAs with zero or one allele of *APOL1* renal risk variants (61). We recently reported the first prospective study to show that *APOL1* is associated with an accelerated rate of progression to ESRD in AA and that the effect of *APOL1* on the risk of disease progression was also present in AA in whom diabetic nephropathy was the underlying cause of CKD (62). In this seminal study, we evaluated the effect of high-risk *APOL1* (two risk alleles) on the composite renal outcome (ESRD, doubling of serum creatinine, or 50% reduction in eGFR from baseline) among 693 black people included in the the AASK and among 2955 white and black patients in the Chronic Renal Insufficiency Study (CRIC). In the AASK study, the primary outcomes occurred in 58.1% of patients in the *APOL1* high-risk group compared to 36.6% in the low-risk *APOL1* group (zero or one *APOL1* allele) yielding an adjusted hazard ratio of 1.88 ($P < .001$) (Table 3). In the CRIC study cohort comprised of 1411 and 1544 black and white patients (Table 3), respectively, we found that the composite renal event rates among diabetics was 5.8 per 100 person-years for all white patients compared to 10.1 per 100 person-years for all black patients ($P < .001$). Among the high-risk *APOL1* group of black patients (two risk alleles), the composite renal event rate was 13.7 compared to 9.5 per 100 person-years in low-risk *APOL1* black patients (zero or 1 risk alleles) ($P < .05$). This study was the first to show the effect of *APOL1* on the risk of kidney disease progression among CKD patients. Among patients with no diabetes, the high-risk *APOL1* group of black patients (two risk alleles) had a composite renal event rate of 7.5 per 100-person years compared to 4.4 per 100-person years in nondiabetic low-risk *APOL1* black patients (zero or 1 risk allele) ($P < .01$). As has been well documented, the rate of composite

TABLE 3
Events Rates and APOL1 *Risk Status in the AASK and CRIC Study*[62]

Variable	With Diabetes				Without Diabetes			
	All White Patients (N = 624)	All Black Patients (N = 722)	Black Patients With *APOL1* Low Risk (N = 610)	Black Patients With *APOL1* High Risk (N = 112)	All White Patients (N = 920)	All Black Patients (N = 689)	Black Patients With *APOL1* Low Risk (N = 531)	Black Patients With *APOL1* High Risk (N = 158)
Duration of follow-up (y)	4.2 ± 2.2	3.8 ± 2.2	3.8 ± 2.2	3.5 ± 2.2	4.9 ± 2.0	4.4 ± 2.2	4.5 ± 2.2	4.2 ± 2.2
Patients with renal events (n, [%])	152 (24.4)	274 (38.0)	220 (36.1)	54 (48.2)	95 (10.3)	155 (22.5)	106 (20.0)	49 (31.0)
Renal event rate (no. per 100-person-y)	5.8	10.1	9.5	13.7	2.1	5.1	4.4	7.5
Incident ESRD-no. (rate/100 person-y)	100 (3.2)	219 (6.5)	177 (6.2)	42 (8.1)	67 (1.3)	122 (3.4)	82 (2.9)	40 (5.0)

$P < .001$ for comparison between all white and all black patients.
$P < .001$ for comparison between *APOL1* high-risk group and the *APOL1* low-risk group.
$P < .01$ for comparison between all white and all black patients.
$P < .05$ for comparison between *APOL1* high-risk group and the *APOL1* low-risk group.
$P < .01$ for comparison between *APOL1* high-risk group and the APOL1 low-risk group.
Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; CRIC, Chronic Renal Insufficiency Cohort study; ESRD, end-stage renal disease

renal events was twice as high among black patients without diabetes (5.1 vs 2.8 per 100-years, $P < .001$) as it was among diabetics as described above.

Just as *APOL1* dramatically increases the risk of kidney disease in AAs, evidence is emerging that *APOL1* renal risk variants may also confer the same deleterious predilection to kidney disease in Africans residing in SSA. In a recent study, Ulasi et al evaluated the relationship between *APOL1* risk variants and the development of kidney disease in a case-control study comprised of 87 participants in Southeastern (SE) Nigeria (63). This study found a high frequency of two *APOL1* risk alleles in the general population of Igbo people in Southeastern Nigeria (23.3%) and found that two *APOL1* risk alleles were present in 66% of patients with CKD yielding an adjusted odds ratio of 6.4 ($P = .0012$) (Fig 1). Of note, the odds ratio of 6.2 for CKD with two *APOL1* risk alleles was after adjusting for the presence of HIV infection. Among AAs, the lifetime risk of developing primary glomerular disease (FSGS) in the presence of two *APOL1* risk alleles is 4%, but the risk increases to 50% in the setting of HIV infection! This suggests that an environmental factor (eg, chronic infection) is essential to dramatically increase the risk of kidney disease due to *APOL1* in both AAs and Africans. The allelic frequencies of the *APOL1* renal risk variants vary widely across SSA (Fig 2). Whether these risk variants lead to the development of CKD and what addi-

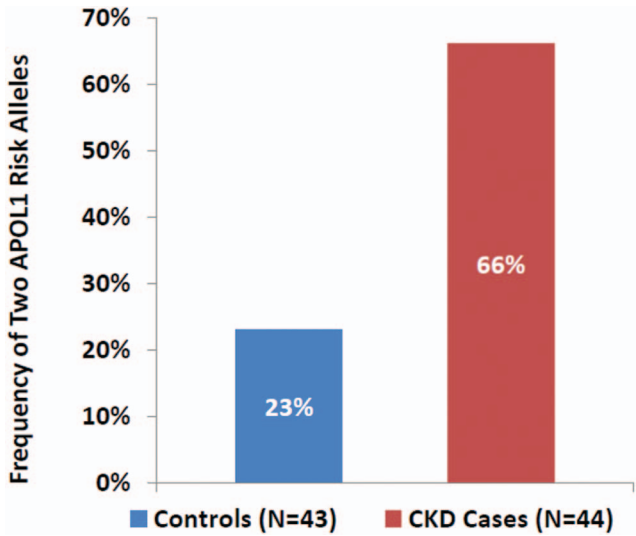

FIG. 1. *APOL1* two-risk alleles carrier frequency among CKD and controls in the Igbo people of Southeastern Nigeria.

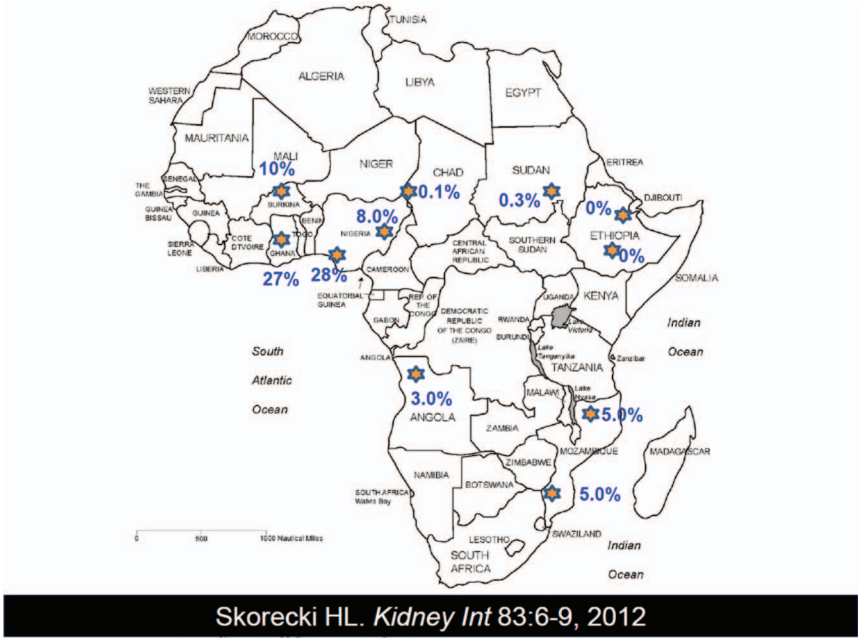

FIG. 2. Distribution of *APOL1* allelic variant frequency in Africa.

tional environmental factors are necessary for disease initiation among people of African ancestry has not been well studied. More importantly, the pathogenic mechanisms of *APOL1* associated nephropathy still remain to be elucidated (64,65).

GLOBAL CKD RESEARCH STRATEGIES

The initial findings implicating *APOL1* risk variants in CKD among AAs and possibly other black populations are consistent and particularly promising in unraveling the catastrophic predilection of people of African ancestry for CKD. However, several questions remain to be answered before these findings can be translated into clinically meaningful preventative and therapeutic tools. How do *APOL1* risk variants contribute to the development and progression of CKD in SSA? Do these risk variants play a role in the development and progression of other infection-associated glomerular diseases such as chronic hepatitis B (HBV) and hepatitis C (HCV) which are highly prevalent in SSA (100 million people in SSA have chronic HBV or HCV infections)? Given the varied allelic frequency distributions, do the biologic effects of the risk variants differ across the

SSA continent with potential implications for variability in risk among AAs according to which region or ethnic group in SSA their African ancestors were extracted? Do the gene-environment interactions differ between the United States and Africa and as well among the various regions of SSA? What are the mechanisms by which *APOL1* causes nephropathy? Finally, what are the pathological implications of additional *APOL1* variants that are being discovered in African populations (for example, *APOL1* G3 variant) and do these new variants have a bearing on the risk of nephropathy among AAs (66)?

We have begun to address these questions with a research project under the Human Heredity and Health in Africa (H3Africa) Initiative developed jointly by the National Institutes of Health and the Wellcome Trust of the United Kingdom. The H3Africa Kidney Disease Study is a case control study of 8000 participants from four African countries (Ethiopia, Ghana, Kenya, and Nigeria) that when combined have a population >320 million (more than one-third of the population of SSA). Nine academic medical centers in these four countries are currently recruiting CKD cases and controls who are between the ages of 0 and 74 years old into the study. Comprehensive phenotypic data will be collected from participants with the following types of kidney disease: hypertensive nephrosclerosis (kidney disease attributed to systemic hypertension); diabetic nephropathy; sickle cell nephropathy; HIVAN; FSGS/minimal change disease; membranous nephropathy; and childhood and adolescent onset nephrotic syndrome. Kidney biopsy material will be obtained for genome-wide mRNA expression profiling and other mechanistic studies from participants who have glomerulopathy. As of March 2014, more than 1000 participants have been enrolled in these studies.

Independent of the H3Africa Kidney Disease Study, intensive effort in basic research investigations aimed at understanding the pathogenesis of *APOL1*- associated nephropathy are ongoing in laboratories across the United States (64,65).

People of African ancestry have endured a disproportionate burden of CKD for more than 3 decades. Discoveries from Genome Wide Association Studies (GWAS) implicating *APOL1* risk variants in the etiology of CKD in these populations hold significant promise if the ongoing clinical and translational research efforts across the globe continue in an intensified and well-orchestrated fashion. More concerted efforts to understand the biology of human evolution from Africa may shed valuable insight into the etiologic mechanisms of other

noncommunicable chronic diseases that now plague significant fractions of the global population.

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DISCUSSION

Nathan, Boston: That has to go down as one of the most interesting talks I've ever heard. I appreciate it very much. My question to you is — on that very interesting study you did on the treatment of hypertension in African Americans where you show these accelerating curves but you don't have a nontreatment group — you sort of said that the treatment didn't prevent renal disease, but compared to what? Compared to nothing? I'd like to know what the curve would have looked like in untreated patients.

Ojo, Ann Arbor: At the time that we initiated this clinical trial in 1993 it would have been unethical not to treat hypertension, at least to less than 140/90 in any population. . .

Nathan, Boston: Excuse me. Yes, I do agree with that. But treatment did do something.

Ojo, Ann Arbor: Treatment did something. It prevented the adverse clinical endpoint in 40% of the participants. But the majority of the participants did not escape the clinical outcome that we are trying to prevent. If one looks at, we know the effect of nontreatment at least historically; we have evidence that if you didn't treat hypertension there would have been a faster rate of progression. What is disturbing about that data

is that we achieved an excellent level of blood pressure control, but yet we had a rate of progression that was three times faster than what is normally seen in the non-Hispanic white population being treated.

Nathan, Boston: Yes. I understand. I just want to get an agreement that the treatment was effective.

Ojo, Ann Arbor: Treatment was effective in that 40% of participants did not develop adverse outcome, but the majority of participants did not do well.

Nathan, Boston: Secondly, I found that, as somebody interested in sickle cell anemia, the relationship that you showed here with the *APOL1* gene was really quite fascinating and maybe has the same basis as the persistence of sickle cell anemia in Africa.

Ojo, Ann Arbor: Thank you for bringing that point up. The parallel is very clear. It's the same picture: a recessive form of the variants. It does not lead to disease. It does not have to protect against malaria whereas if you have two copies of the alleles, you develop sickle cell disease, so in this case, you develop kidney disease.

Zeidel, Boston: Wonderful talk. This really illustrates, as a quick comment, the enormous importance of both basic research and clinical epidemiological research: the ability to take the *APOL1* discovery and rapidly identify where it matters. And it is because of all of the enormously important work that had been done previously in the epidemiology. I think going forward it will be critical for us to understand what *APOL1* does, how it works, and how to block it. Because, of course, that will be game-changing therapy. Any thoughts though as to what we might be able to do if we could block *APOL1*? What would we be doing in Africa with it given the fact that the trypanosome is there? What are your thoughts about that?

Ojo, Ann Arbor: Thank you very much for your comments. I could not agree with you more that this is a classic example of taking the benefit of basic science and trying to exploit it in the clinical research arena. So unfortunately in many parts of Africa, there was a concerted effort to try and eradicate the tsetse fly which is responsible for transmitting trypanosomiasis, and that effort was successful to a large extent in the late 1970s and early 1980s. If you look at the epidemiology of African sleeping sickness now, it parallels places in Africa where there is political instability or war, because that is when the tsetse fly is able to repopulate and transmit disease. So if one is able to block the *APOL1*, I think that the impact for that spread of the parasite will be limited, in that it would be possible to implement a less aggressive eradication controlled program in those loci — geographic loci in Africa — where there is a resurgence of the endemicity of the tsetse fly and the parasite.

Winchester, New York: For many years, we believed that there was a thrifty gene that allows the survival of the slave trade to come to the shores of America. That the people who retained salt were able to survive the journey. Do you think there is a co-association between *APOL1* and the cell gene, the thrifty gene? The comment is also that in the AASK trial I believe that the sodium is not controlled.

Ojo, Ann Arbor: In the AASK trial we took some effort, albeit very modest, to control dietary sodium intake. What we do have is evidence of sodium construction from 24-hour urine sodium collection. We confirmed in the AASK trial, what has been demonstrated elegantly by a group of investigators in the Netherlands, that response to ACE inhibitor in terms of blood pressure reduction is a function of salt intake, and that those who are at the upper end of salt intake do not have significant blood pressure reduction. But in the AASK trial, in everybody, we achieved excellent blood pressure reduction. I think there is an opportunity to further explore the role of salt consumption in this population as well as how *APOL1* is involved in that. In studies that we are doing in the five countries in Africa, we are doing comprehensive phenotype data collection including dietary salt intake, and we are able to see how the patterns of dietary salt intake interact

with *APOL1* variants. That is one of the gene environment interactions that will be important to seek this out to better understand the role of these variants.

del Rio, Atlanta: Can you comment about the *APOL1* gene and HIV-associated nephropathy (HIVAN) and therefore are you going to also be doing this in Africa where there is a lot of HIV? How are you incorporating the relationship with HIV nephropathy into the study that you are doing?

Ojo, Ann Arbor: So, as you know, one of the studies that looked at *APOL1* was in people with HIV nephropathy which has one of the highest odds ratios of disease. So in the cohort that we are developing in Africa, we have 500 cases of HIV nephropathy with biopsy, is what we hope to collect. And in those people my colleagues at Michigan, Matthias Kressler and his group, will be doing MRA expression profiles looking at functional pathways stratified according to *APOL1* genotype in the biopsy tissue of those HIV nephropathy patients to try and understand the mechanism by which *APOL1* interacts to lead to increased risk of HIV nephropathy.

Luke, Cincinnati: I think the work on renal susceptibility genes is extremely important in what you are doing. I have two caveats though. I did head, as you probably know, the Safety Committee for this study, the AASK study. The mean serum creatinine was 2, the mean GFR —measured GFR not EGFR — was 45, and there was a 90-mg median protein excretion per day, which is very different from focal sclerosis. So my caveat is really that the treatment didn't start early enough. The second caveat, calling this disease hypertension-associated is very dangerous. Only half of people — and probably higher than that, in African-Americans — are treated to target at present. If you keep talking about hypertension-associated, we may diminish the interest in treating the blood pressure effectively, since blood pressure treatment is the main thing in preventing stroke, cardiovascular disease, and is still very important in slowing the course of chronic renal disease. No one denies that the most important thing at the present stage of our knowledge is to treat hypertension and slowing the progression of the GFR elevation. So I would ask the renal community to continue to describe it as hypertensive nephrosclerosis. That will change when you come up with understanding the process by which *APOL1* works, which we don't know, and you have a therapeutic thing to do.

Ojo, Ann Arbor: Thank you very much, Dr Luke. I do not mean to say at all, that treatment for blood pressure is futile. I think in people who are not adequately treated, the rate of progression is even faster. I agree with you completely that the term hypertensive-associated nephropathy is imprecise, and that imprecision is driven because of our state of knowledge that is limited. We do not know what the biologic mechanism is. Plus the fact that, as you very well know, there are a lot of people who present with hypertension with some renal insufficiency who may not have hypertension. Hypertension here would be secondary to reduction in renal function, and I share your concern in being careful in moving this forward.

Wing, Providence: I wonder if you want to comment on the complexity of trypanosomiasis in Africa? So there are two major organisms, *T. brucei* and *T. rhodesiense* in East Africa. One of the major effects of trypanosomiasis is not on humans; it is on cattle. So it doesn't allow populations to exist in areas because they can't raise their cattle. And resistant cattle have also been identified and are used in some parts of Africa. I wonder if you want to comment on any of those aspects and if anything can be learned in terms of the heterogeneity of trypanosomiasis in Africa?

Ojo, Ann Arbor: Thank you very much. So, as you pointed out, there are two major subspecies; the gambiense which is endemic in West African countries and *T. rhodesiense* which is more localized to the Eastern part of the continent. The *T. rhodesiense* tends to cause the acute form of sleeping sickness, whereas *T. gambiense* causes the more chronic form of the disease. The *APOL1* with variants that lyses the trypanosome

is only effective against the West African form. So if you look at the allelic frequency of *APOL1*, it is highest in West Africa where there is no *T. rhodesiense*. So possibly the evolutionary selection had been effective in helping to eradicate rhodesiense from West Africa, leaving behind the *T. gambiense*, for which the risk variants do not have a trypanosome lytic factor. As to the relationship between the *T. brucei* that has the cattle as the natural host, I think that the pattern of distribution of disease follows the geographic or the climate conditions in different parts of Africa. Places where there is a lot of humidity and overgrown shady areas is where the tsetse fly glossina that transmits the parasite tends to live and so you tend to have infection in areas that are more shaded with heavy trees rather than savannah areas in different parts of East Africa.